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ORIGINAL ARTICLE

Comparative study between the effects of Nalbuphine, Propofol, and Ondansetron for control of intrathecal opioid induced pruritus in parturients after Cesarean Section: Randomized Controlled Trial.

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ABSTRACT

Background: Controlling intrathecal opioid induced pruritis is considered a significant challenge to anesthetists. The aim of this study was to compare the effects of Nalbuphine, Propofol, and Ondansteron in controlling intrathecal morphine induced pruritis to find out the best one with least side effects.

Methods: 248 parturients with moderate to severe pruritus after spinal anesthesia with 2 mg morphine added to 10 mg bupivacaine for cesarean section were included. According to the used drugs, they were randomized into four equal groups: Control group (Group C) received 10 ml of normal saline (as Placebo) IV, Nalbuphine group (Group N) received 4mg (0.2 ml) of 2% Nalbuphine diluted up to 10 ml with normal saline IV, Propofol group (Group P) received 20 mg (2 ml) of 1% Propofol diluted up to 10 ml with normal saline IV, and Ondansetron group (Group O) received 8 mg (4ml) of 0.2% Ondansetron diluted up to 10 ml with normal saline IV. The effects of interventional drugs in controlling pruritus and associated side effects were evaluated in each group.

Results: Statistically, parturients' characteristics and pre-treatment pruritus scores distribution were comparable. The post-treatment pruritus scores distribution was highly significant decreased in Nalbuphine group and post-treatment success rate was highly significant in Nalbuphine group (93.6%) than in Propofol (71%) and Ondansetron groups (53.2%). No statistical significant difference was noticed regarding the adverse events in the studied groups.

Conclusion: Nalbuphine (4mg) was superior to both Propofol (20mg) and Ondansteron (8mg) for treatment of intrathecal morphine-induced pruritus after cesarean section.

Keywords: Pruritus, intrathecal morphine, Nalbuphine, Propofol, Ondansetron.

INTRODUCTION

Adding opioids to intrathecal local anesthesics is the most frequent anesthetic technique used for cesarean section. Intrathecal morphine is used to augment and prolong both intra- and post-operative analgesia. However, many side effects of spinal morphine have been reported including pruritus, urine retention, nausea, vomiting, and respiratory depression [1]. Pruritis is the commonest side effect with an incidence of 69% in non-pregnant versus 83% in postpartum patients [1, 2]. The susceptibility to intrathecal opioid induced pruritis seems to increase in pregnant females than other patients with the incidence may reach up to 100% which may be due to the interaction between estrogen and opioid receptors [1-3].

Pruritus is a subjective undesirable tingle irritating sensation which induces scratching. It has a negative effect on the parturient anesthesia and delivery experience and may interfere with the mother-baby bond. Although many hypotheses have been discussed, the exact cause of neuraxial opioid induced pruritus is still hazy. Stimulation of micro-opioid, 5-hydroxytryptamine3 (5HT3) and dopamine 2 receptors in the dorsal horn and medulla may be involved in the pathogenesis.

Spinal inhibitory pathways and Prostaglandins may also be included [4-7]. This makes it extremely hard to outline powerful medication regimens for such cases and it remains a challenge to all anesthetists. Numerous drugs have been studied with a little evidence of their efficacy. Opioid antagonists, opioid agonist-antagonists, propofol, 5-hydroxytryptamine3 (5-HT3) (serotonin) receptor antagonists, antihistamines, and non-steroidal anti-inflammatory drugs have been utilized [1, 2].

There is a promising evidence support the use of Nalbuphine as an opioid agonist-anatgonist [8] and possibly Ondansetron, a selective serotonin type 3 receptor antagonist could be used to treat neuroaxial opioid induced pruritis [9]. Also, sub-hypnotic dose of Propofol was found to have antipruritic action by inhibiting the posterior horn transmission in the spinal cord [10]. The aim of this study was comparing the effects of Nalbuphine, Propofol, and Ondansetron for control of intrathecal morphine induced pruritus in parturients after Cesarean Section to find out which one is the best with least side effects.

PARTURIENTS AND METHODS

This study is prospective randomized double blind controlled clinical trial. It was carried out on 248 out of 310 ASA physical status class I and II parturients who developed grade 3 & 4 pruritus after receiving intrathecal 2 mg morphine added to 10 mg bupivacaine spinal anesthesia for cesarean section (figure 1). The age of these parturients ranged from 18 – 40 years, their body weight ranged from 55 to 85 kg and their height ranged from 150 to 170 cm. This study was achieved in the period from April 2018 to March 2019 at Zagazig University Hospitals, after obtaining a written informed consent from all participants or their legal guardians and approval of our institutional review board (The research ethical committee of Faculty of Medicine, Zagazig University). This study was performed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Ppatients with history of allergy to the studied drugs, pruritogenic diseases, on opioids treatment, hepatic, renal or cardiac disease were excluded from this study.

On arrival to the post anesthesia care unit (PACU), with recording of vital signs, the onset and degree of pruritus were assessed by using pruritus score where 1 equals no pruritus, 2 is mild pruritus with no need to scratch just rubbing and treatment is not needed, 3 is moderate pruritus with a need to scratch and treatment is needed, and 4 equals severe form pruritus with high need to scratch that requires treatment [11].

Participants whose pruritus score was 3 or 4 were randomly assigned to one of four equal groups by using computer generated random number. The assignment belongs each generated number was sealed in an opaque envelope to be opened by blinded anesthetist who will give the studied drugs and record the data. The studied drugs were prepared in opaque covered syringes by a nurse not involved in further data handling. Opaque covered syringes were used to avoid anesthetist and patients' recognition of the white color of Propofol. The four assigned groups were, Control group (Group C) which received 10ml of normal saline IV as placebo, Nalbuphine group (Group N) received 4mg (0.2ml) of 2% Nalbuphine diluted up to 10 ml with normal saline IV (Nalufin®; ampoules 20mg/ml; Amoun pharmaceutical, Egypt), Propofol group (Group P) which received 20 mg (2 ml) of 1% Propofol diluted up to 10 ml with normal saline IV (Diprivan®; ampoules 10 mg/ml; Zeneca, Macclesfield Chesshire, UK), and Ondansetron group (Group O) which received 8 mg (4 ml) of 0.2% Ondansetron diluted up to 10ml in normal saline IV (Zofran; ampoules 8 mg/4ml; Glaxo SmithKline Manufacturing S.P.A. Parma, Italy).

Sample Size Calculation: The sample size was to be 49 patients per group to detect a decrease in the incidence of pruritus from 70% to 40% based on previous study done by Liao et al. [8] with allowing 0.05 type I error of, 85% power and 95% confidence interval using Open Source Epidemiologic Statistics for Public Health, Version 3 available at www.OpenEpi.com.We decided to recruit 62 patients per group to account for possible study dropouts or data loss.

In this study, the following data were detected and recorded in each groups: Demographic data and pre-treatment puritus score distribution in the participants of the four tested groups which include age, body weight, body height, ASA physical status classes distribution, pre-treatment pruritis scores distribution, Post-treatment pruritus distribution in each group, and post-treatment success rate that was defined as the percent of participants with pruritus scores less than 3. As well as, treatment failure was defined as persistence of the pre-treatment pruritus score to a level of 3 or 4. Parturients with failed treatment were given 0.04 mg of naloxone increments IV to overcome the pruritic effect of intrathecally administered morphine.

All enrolled parturients were assessed for the onset of pruritus in PACU and along with patient's complaint for up to 24 hours after cesarean section as well as the associated side effects of the tested drugs.

Partuients were assessed for suspected side effects for 24 hours after cesarean section including sedation which was assessed by using Ramsay sedation scale from 1 to 6 (1 means that patient is anxious, agitated or restless, 2 means that patient is cooperative, oriented, and tranquil, 3 means that patient responds to commands only, 4 means that patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5 means patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, and 6 means patient exhibits no response.). Also, patients were evaluated for nausea and vomiting which was recorded as 0 = no nausea or vomiting; 1 = mild nausea; 2 = intense nausea; 3 = vomiting [11]. Patients were considered as having nausea / vomiting only in the presence of score ≥ 2 and were treated with metoclopramide 10mg IV as well as, other associated side effects such as pain on injection of the study drugs, shivering, dizziness and respiratory depression were recorded.

Statistical Analysis: Statistical Package for Social Science for windows version 18.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Continuous variables were expressed as mean ± SD while categorical variables were expressed as number and percentage. Normality of Continuous variables was checked using Shapiro-Wilk test. We used one way ANOVA test to compare more than two groups of normally distributed data. Chi-square test was used to compare the Percent of categorical variables. P value was set at < 0.05 for statistically significant.

RESULTS

310 parturients were given intrathecal morphine in addition to spinal anesthesia for cesarean section during our study period. 248 parturients met our inclusion criteria and developed pruritus grade 3 and 4 (The incidence of pruritus was 80%) were enrolled in this study (figure 1).

Statistically, parturients' characteristics (age, body weight, body height and ASA physical status classes distribution) and pre-treatment pruritus score distribution in the four tested groups were comparable (Table 1).

the post-treatment pruritus scores distribution among the four tested groups was statistically highly significant in Nalbuphine, Propofol, and Ondansteron groups than in control group with significant improvement in pruritus scores and increasing number of patients with pruritus score 1 and 2 in Nalbuphine group than in Propofol and Ondansteron groups (table 2)

Statistically, the post-treatment success rate in each of Nalbuphine, Propofol, and Ondansetron groups was significantly higher than that in control group. The post-treatment success rate was highly significant in Nalbuphine group (93.6%) than in both Propofol (71%) and Ondansetron groups (53.2%). The treatment success rate was significantly more in Propofol group (44 of 62 paturients; 71%) than in Ondansetron group (33 of 62 parturients; 53.2%) (Table 3).

No statistical significant difference was noticed regarding the adverse events in the studied groups. No significant difference in the sedation score, shivering, dizziness and pain on injection. No cases of respiratory depression were noticed in the four groups. There was significant decrease in the incidence of nausea and vomiting in Ondansetron group compared to the other three groups. Metoclopramide treatment for vomiting was less in Ondansetron group (Table 4).

Table 1: Demographic data and pre-treatment puritus score distribution in the participants of the four tested groups

Characteristics	Group C (n= 62)	Group N (n= 62)	Group P (n=62)	Group O (n= 62)	P value
Age (years)	22.61± 2.91	23.46±2.44	23.58 ± 2.79	23.52 ± 2.44	0.142
Weight (kg)	68.62 ± 10.89	68.68± 10.28	65.38±8.70	67.80± 9.04	0.201
Height (cm)	162.17± 4.45	162± 5.00	160.46± 4.42	160.86± 4.89	0.118
ASA Physical status					
ASA I Number (%)	29(46.8%)	30(48.4%)	34(53.6%)	38 (62.5%)	0.11
ASA II Number (%)	33(53.2%)	32(51.6%)	28(46.4%)	24(37.5%)	0.11
Pre-treatment pruritus score					
Score 3 Number (%)	30 (48.4%)	28 (45.2%)	40 (64.5%)	29(46.8%)	0.11
Score 4 Number (%)	32 (51.6%)	34 (54.8%)	22 (35.5%)	33 (53.2%)	0.24

Data were expressed as mean ± SD, number and percent.

Group C = Control group, Group N= Nalbuphine group, Group P = Propofol group, Group O = Ondansteron group.

n = Total number of patients in each group.

P < 0.05 is significant. P < 0.001 high significant difference

Tables 2: Post-treatment pruritus scores distribution in the four tested groups.

Variable	Group C (n= 62)	Group N (n= 62)	Group P (n=62)	Group O (n= 62)	P value
Post-treatment score					
Score 1	0 (0%)	30 (48.4%)*	23 (37.1%)	10 (16.1%)	<0.001
Score 2	0 (0%)	28 (45.2%)*	21 (33, 9%)	23 (37.1%)	<0.001
Score 3	30 (48.4%)	2 (3.2%)*	10 (16.1%)	15 (24, 2%)	<0.001
Score 4	32 (51.6%)	2 (3.2%)*	8 (12.9%)	14 (22.6%)	<0.001

Data were expressed as mean ± SD, number and percent.
Group C = Control group, Group N= Nalbuphine group, Group P = Propofol group, Group O = Ondansteron group.
n = Total number of patients in each group.
P < 0.05 is significant. P < 0.001 high significant difference
* pruritus scores was statistically highly significant decreased in Nalbuphine group

Table 3: Post pruritus treatment success rate in the four tested groups.

Variable	Group C (n= 62)	Group N (n= 62)	Group P (n=62)	Group O (n= 62)	P value
Parturients with pruritus scores < 3 Number (%)	0 (0)	58 (93.6%)*	44 (71%)	33 (53.2%)	<0.001

Data were expressed as number and percent.
Group C = Control group, Group N= Nalbuphine group, Group P = Propofol group, Group O = Ondansteron group.
n = Total number of patients in each group.
P < 0.05 is significant. P < 0.001 high significant difference
*success rate was statistically highly significant with Nalpuphine treatment than Propofol and Ondansteron.

Table 4: The incidence of the various associated side effects of the tested drugs.

Variable	Group C (n= 62)	Group N (n= 62)	Group P (n=62)	Group O (n= 62)	P value
Increased N/V score Number (%)	22 (35.5%)	14 (22.6%)	18 (29%)	5 (8.1%)*	0.0027
Increased sedation Number (%)	7 (11.3%)	6 (9.7%)	7 (11.3)	8 (12.9%)	0.956
Shivering Number (%)	6 (9.7%)	5 (8.1%)	7 (11.3%)	6 (9.7%)	0.947
Dizziness Number (%)	7 (11.3%)	5 (8.1%)	6 (9.7%)	6 (9.7%)	0.939
Pain on injection Number (%)	1 (1.6%)	2 (3.2%)	2 (3.2%)	0 (0%)	0.887
Respiratory depression Number (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Metaclopramide for vomiting treatment Number (%)	14 (22.6%)	16 (25.6%)	15 (24.2%)	0 (0%)**	< 0.001

Data were expressed as Number and percentage
N = Total number of patients in each group.
N/V score = Nausea/ Vomiting Score
P < 0.05 is significant. P < 0.001 high significant difference
*N/V score was statistically significant lower in Onadersteron group
**Metaclopramide for vomiting treatment was high statistical significant less in Ondansteron group.

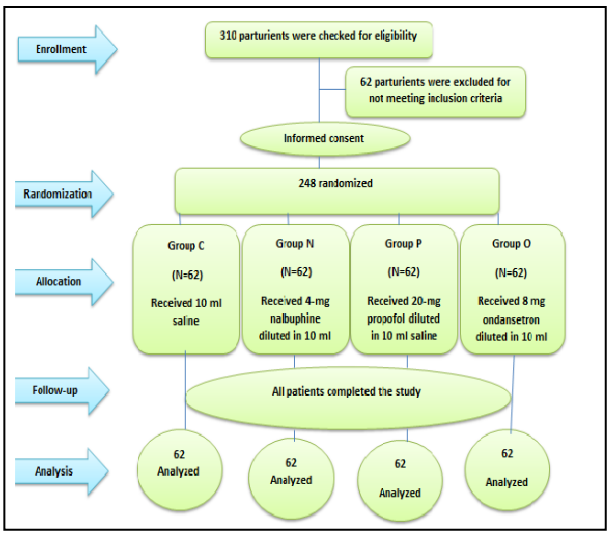

Figure 1: Study flow chart

DISCUSSION

Pruritus is the commonest adverse effect after intrathecal opioids and considered one of irritating issues for parturients. It has a negative impact on the patient satisfaction and quality of life. As a result of its complicated unclear mechanism, the treatment of intrathecal morphine induced pruritis remains a challenge and many pharmacological interventions have been studied with only few literatures support their effectiveness [12]. We investigated the effectiveness of 3 different drugs with different mechanisms of action (Nalbuphine, Propofol, and Ondansteron) on treating intrathecal morphine induced pruritis in partuients undergoing cesarean section.

Our study demonstrated a high incidence of pruritus grade 3& 4 in parturients after intrathecal morphine administration that reached 80%. This high incidence was consistent with other previous studies [3, 13]. Data from previous studies revealed that the incidence of pruritus after administration of opioid is 2% to 20% when it is given orally [14, 15], 10% to 50% when it is given intravenously [16, 17], and 30% to100% when it is given by spinal or epidural rote [13]. The alternation of opioid receptors by estrogen during pregnancy and the more cephalic spread of the intrathecal drug by pregnancy may explain the high incidence of pruritis in this group of patients [18].

The current study showed that the success rate in Nalbuphine group was significantly greater than in Propofol and Ondansetron groups (93.6% vs 71% and 53% respectively). This is in agreement with Jannuzzi who concluded that low dose Nalbuphine had a greater effectiveness in the treatment of opioid induced pruritus compared with placebo, Diphenhydramine, Propofol, and Naloxone without attenuation of the analgesia or rising of the sedation score [19].

Numerous studies have proved the antipruritic effects of mu-receptor antagonists such as Nalbuphine and Naloxone. Ko et al. found that the administration of mu-opioid receptor agonists as fentanyl, alfentanil, and remifentanil caused pruritus whereas administration of kappa or delta receptor agonist did not. They found also that pruritus was alleviated by mu- receptor antagonist and discovered that opioid-induced pruritus is primarily mediated through central mu-opioid receptors because the quaternary form of naltrexone that can't cross the blood-brain can't attenuate opioid-induced scratching [20]. Additionally, many other studies showed that kappa-receptor agonists can inhibit neuraxial opioid-induced pruritus [21, 22, 23]. Nalbuphine is a mixed kappa-receptor agonist and mu-receptor antagonist and this would explain its antipruritic effect via action on the mu- and kappa-receptors [24].

Pruritus from neuraxial opioids may also be related to the stimulation of nociceptive and non-nociceptive neurons in the anterior and posterior spinal horns [25, 26] this may explain the ability of Propofol to control 71% of pruritis in our study as Propofol inhibits the posterior horn of the spinal cord. The superiority of Nalbuphine over Propofol in our study is supported by Charuluxananan et al [10].

Various studies have proposed alternation of serotonin-type 3 (5-HT3) receptors by opioids as a probable mechanism for pruritus. The high density of both mu-opioid and 5-HT3 receptors in the dorsal part of the spinal cord and the trigeminal nerve nucleus raised this possibility [7, 15, 22]. Indeed, several studies have reported success with

preventing itching with I.V Ondansetron [9, 18, 22, 25], while others have denied [26, 27]. Our results showed the ability of Ondansetron to alleviate pruritus in 53% of cases. With our results, the systematic review of 15 randomized controlled trials indicated that prophylactic treatment with a single I.V bolus of 5-HT3 receptor antagonists may lead to a significant decrease in the incidence and intensity of pruritus after neuraxial opioid administration, mainly when morphine is used [7]. Also, we found that the use of Ondansetron reduced the opioid induced post-operative nausea and vomiting which is in agreement with Koju et al. [11].

The doses of our investigated drugs were chosen according to the previous studies; for Nalbuphine (4 mg) had been used successfully in a similar population in the study by Somrat et al. [29], 20mg of Propofol was according to the study of Borgeat et al. [30], and 8mg of Ondansetron was according to the study by Stirnemann and Borgeat [31].

Our results showed non-significant adverse events from the three studied drugs, that were also documented in other previous studies [10, 18, 22, 29].

However, this study was limited by the inclusion of only parturients undergoing cesarean section. Therefore, randomized controlled trials among non-parturients to avoid the potential effects of gestational hormones on pruritus development as well as studies to investigate the efficacy of these drugs in other surgical populations including males are highly recommended. Also, the results may differ if different or repeated doses of tested drugs were used. Consequently, examining dose dependant effects would be worthwhile to perform among these populations in the future. Also, it worth mentioning that, we choose to give the tested drugs after delivery to treat the developed pruritus while if the drug intervention occurred before intrathecal morphine injection to prevent pruritus development would be of valuable importance to study in the future.

CONCLUSION

In conclusion, when comparing the effects of Nalbuphine, Propofol, and Ondansteron for control of intrathecal morphine induced pruritis in parturients after cesarean section, Nalbuphine (4mg) was superior to both Propofol (20mg) and Ondansteron (8mg) for treatment of intrathecal morphine-induced pruritus. It provides greater success rate than Propofol and Ondansetron (93.6% vs 71% and 53% respectively) with minimal side effects. Therefore, we support the use of single dose of 4mg Nalbuphine IV in pruritis control in partuients after cesarean section.

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Conflicts of interest
There are no conflicts of interest.

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